PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Ryuichi MORISHITA , et al.

Docket No: Q64360

Appln. No.: 09/856,374

Group Art Unit: 1632

Confirmation No.: 8301

Examiner: Qian Janice LI

Filed: May 21, 2001

For: GENE THERAPY FOR CEREBROVASCULAR DISORDERS

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a copy of an executed Declaration Under 37 C.F.R. §1.132 signed by Ryuichi MORISHITA. Please consider this Declaration along with the Amendment Under 37 C.F.R. § 1.114(c) filed April 6, 2004 in the above-identified application.

Respectfully submitted,

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WASHINGTON OFFICE
23373
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Date: May 11, 2004

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DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I. Ryuichi MORISHITA, hereby declare and state:

THAT I am one of the inventors of the invention disclosed and claimed in the above-identified application;

THAT I am a citizen of JAPAN;

THAT I received the degree of medical doctor in 1986 from Osaka University;

THAT I have been employed by Osaka University since April 1, 1996, where I hold a position as professor, with responsibility for Division of Clinical Gene Therapy;

THAT I am fully familiar with the above-identified U.S. application (hereinafter referred to as "present invention" for brevity);

THAT I have read and am fully familiar with the art cited against claims of the above-identified U.S. application (hereinafter referred to as "present application" for brevity);

I SUBMIT herewith this Declaration in support of the non-obviousness of the present invention:

A person skilled in the art could not have reasonably expected that injection of VEGF and HGF genes into the subarachnoid space would result in significant levels of protein expression in the brain as achieved by the present invention, given the poor efficiency of gene transfection in the central nervous system. Further, because of the fundamental differences between diseases of the brain and diseases of other organs, the heart and skeletal muscle effects described in Isner and Morishita et al. would not have led a person skilled in the art to reasonably expect that VEGF and HGF gene therapy would be an effective treatment for cerebral occlusive disease as achieved by the present invention.

Surprisingly, the present inventors have found that injection of VEGF and HGF genes into the subarachnoid space results in significant levels of protein expression in the brain, and that VEGF and HGF gene therapy are effective treatment for cerebral occlusive disease.

Before the present invention was made, a person of ordinary skill in the art would not have predicted that transfection of HGF and/or VEGF genes into the subarachnoid space would result in effective levels of protein expression. See, e.g. Youichi Saitoh, et al., *Gene Therapy for Ischemic Brain Diseases*, Current Gene Therapy (2003), vol. 3, no. 1, pp. 49-58. Further, prior to the present invention, it was acknowledged that the brain is fundamentally different from other organs such as heart, and that brain diseases are difficult to treat. Id.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment. or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2004/04/27

Dr. Ryuichi MORISHITA